Mechanisms of Noradrenergic Modulation of Dentate Gyrus Long-Term Plasticity

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1. INTRODUCTION

Since D. O. Hebb (1949) inaugurated the search for cellular mechanisms underlying brain function and behavioral plasticity, many strategies and model systems have been employed. One fruitful strategy has been the search for specific chemical transmitters able to modulate firing patterns of neurons in specific pathways for long periods of time. A promising model system has arisen from the discovery that brief, high-frequency stimulation of afferent pathways in the hippocampus leads to long-lasting enhancements of neuronal excitability whose persistence approach that of conditioned behavior (Bliss and Gardner-Medwin, 1973; Douglas and Goddard, 1975). The enhancement of evoked potentials after one such tetanus has been termed long-term potentiation (LTP; Bliss and Lømo, 1973; Schwartzkroin and Wester, 1975; Alger and Teyler, 1976), and repeated application of such stimulation yields the seizure state known as kindled epilepsy (Goddard et al., 1969). In both cases, the location of such long-lasting plasticity in a brain structure implicated in memory processes (Milner, 1972; Berger, 1984), its production by brief (a few seconds) stimulation within the physiological range (10–400 Hz), and the long duration of the changes (months in vivo) all led to extreme interest in their underlying mechanisms (Swanson et al., 1982).

It seems possible that long-lasting changes in excitability induced by repetitive stimulation may mimic the requirement for repetition observed in experience-dependent memory, whereas neuromodulators that modulate the strength and duration of such changes may correspond to the capability for associative learning. Such a potential modulatory neurotransmitter is the monoamine norepinephrine (NE), which has been strongly implicated both in memory processes (Stein et al., 1975; Crow and Wendlandt, 1976; Mason and Iversen, 1977; Everitt et al., 1983; Zornetzer, 1984) and hippocampal plasticity (McIntyre and Edson, 1982; Bliss et al., 1983; Stanton and Sarvey, 1985a). Here we...
consider the cellular mechanisms of action of NE on hippocampal neurons and how these may relate to noradrenergic modulation of hippocampal LTP and behavioral plasticity.

2. NOREPINEPHRINE AND EXPRESSION OF LONG-LASTING HIPPOCAMPAL PLASTICITY

Evidence for a functional role for NE in hippocampal plasticity began with studies showing that prior depletion of NE markedly impairs perforant path LTP in the dentate gyrus both in vivo (Bliss et al., 1983) and in isolated hippocampal slices (Stanton and Sarvey, 1985a). The slice work indicated a hippocampal site of action as well as specificity within the hippocampus, since LTP in field CA1 was unaffected. Furthermore, it was shown that β₁-receptor stimulation of cAMP is the most likely mediator of these effects (Stanton and Sarvey, 1985a–c).

Of equal interest was the finding that a brief application of NE in the absence of high-frequency electrical stimulation also produced a long-lasting potentiation of perforant path synaptic transmission in the dentate gyrus (Neuman and Harley, 1983; Stanton and Sarvey, 1985c). This potentiation showed similar area specificity and also appeared to be β₁-receptor mediated. An example of NE-induced long-lasting potentiation in the dentate gyrus is illustrated in Fig. 1.

Although noradrenergic modulation of long-term hippocampal plasticity is indicated, the mechanisms of action of NE in controlling excitability and information throughput in the hippocampus remain to be worked out. Doing so promises both to shed insight on normal hippocampal function and to suggest pharmacological interventions that may be able to alleviate memory deficits.

3. NOREPINEPHRINE ENHANCEMENT OF STIMULUS-EVOKED CHANGES IN EXTRACELLULAR CALCIUM AND POTASSIUM CONCENTRATION IN THE DENTATE GYRUS

In view of the role indicated for NE in LTP elicited by high-frequency stimulation, we employed ion-selective microelectrodes to measure the decreases in extracellular Ca²⁺ concentration (Δ[Ca²⁺]₀) and increases in extracellular K⁺ concentration (Δ[K⁺]₀) as-

![Figure 1. Norepinephrine (NE)-induced long-lasting potentiation of perforant-path-evoked population responses recorded in the dentate gyrus of hippocampal slices. Evoked field potentials are shown immediately prior to bath application of NE (control), after a 15-min NE application [NE (50 μM)], and after subsequent 30-min drug-free wash (wash). This long-lasting potentiation typically lasts for many hours. (Arrows denote single stimulus artifacts.)](image-url)